Formulation, Development and Evaluation of herbal transdermal patch using different bioactive compounds for acute and chronic wound healing.

SYNOPSIS

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INTRODUCTION

The transdermal patch is a drug delivery system (DDS) for wound healing that has been used for a long time. The drug delivery technology for skin disorder has evolved from ointment, cream and gel to the transdermal patch because of its lots of advantages over other delivery system such as; it allows constant dosing which prevent the fluctuation of drug level in blood stream and it is also non-invasive. Transdermal drug delivery system has many advantages over conventional modes of drug delivery, provides a controlled rate of release of medicaments, avoids hepatic metabolism, ease of termination and long duration of action. Transdermal drug delivery system (TDDS) is topically administered medicaments in the form of patches or semisolids (gels) that deliver drugs for the systemic effects at a predetermined and controlled rate.

The processes for drug transdermal permeation start with sorption by the stratum corneum, then drug penetration through the viable epidermis, and finally drug uptake in the dermal capillary layer. Membrane permeation controlled, matrix diffusion controlled, adhesive dispersion controlled, and microreservoir/microsealed dissolution controlled systems are the four types of transdermal drug delivery systems. Transdermal route has gained more attention in drug delivery due to its flexibility and convenience in comparison to other routes of delivery and it is one of the suitable, convenient, safe and economic ways to deliver drug. A medication is given to the inside of a patch that is worn on the skin for an extended period of time in a reasonably high dosage. The medication enters the bloodstream immediately through the skin through a diffusion process. Because the medication has a high concentration on the patch but a low concentration in the blood, it will continue to diffuse into the blood for a long time, keeping a steady drug concentration in the blood flow.

A wound is a type of injury in which the skin is torn, cut, or punctured (an open wound), or a contusion is caused by blunt force trauma (a closed wound). Wound can be ranges from a simple skin damages to serious damages which involves deep cut and result in chronic wound. Serious damage can extend deep into subcutaneous tissue, causing destruction to tendons, muscles, arteries, nerves, parenchymal organs, and bones, among other structures. The process of restoring the physical integrity of internal or exterior body structures is known as wound healing. The healing process of a skin wound follows a predictable pattern; inflammatory stage, fibroblastic or proliferative stage and maturation or remodeling stage. In proliferative phase angiogenesis,

collagen deposition, granulation tissue formation, epithelialization, and wound contraction occurs. Angiogenesis means formation of new blood vessel growth from endothelial cells. Fibroblasts expel collagen and fibronectin to generate a new, provisional extracellular matrix during fibroplasia and granulation tissue development. Following that, epithelial cells crawl across the wound bed to cover it, and myofibroblasts, which grab the wound borders and contract using a mechanism similar to that of smooth muscle cells, compress the wound.

Wound care and appropriate treatment not only promote healing, but also reduce the cost of hospitalization and save the patient from amputation or other major health complications. Wound care currently includes antibiotics, wound debridement (enzymatic, biologic, surgical, and irrigation), topical therapy (growth factors, antiseptics, and antimicrobials agents), and wound dressings (film, hydrogel, foam, alginate, hydrocolloids). These wound-healing techniques are intended to improve the wound-healing environment while also preventing infection. However, there is insufficient evidence to back up and justify any of these policies. The different methods and approaches are being tried and used to achieve shorter wound healing time. Hence, there is need for safer and effective wound-healing agents. Because now a day, non-healing and chronic wounds are a significant healthcare problem in medical practice.

Plant extracts' wound-healing properties can be linked to their phytoconstituents' antibacterial, anti-oxidative or free radical scavenging properties, as well as mitogenic activity, angiogenesis, collagen creation, and DNA synthesis, which are all triggered by their phytoconstituents.

Giloy or Guduchi (*Tinospora cordifolia*) is a very important medicinal plant in Ayurvedic system of medicine irrespective of the part of the plant; it is used in the medicines since ancient time for the treatment of tuberculosis, jaundice, ulcer, fever, diabetes, skin diseases etc. Tinospora is a genus comprising 35 species in the Menispermaceae family, including seven species found in tropical Africa, three in southern Africa, two in Madagascar, and 23 in Australia, Asia, and the Pacific. Bioactive chemicals like as alkaloids, phenolic molecules, and related compounds are abundant in the Tinospora family. In the present time, species of this plant has been subjected for numerous chemical, pharmacological, preclinical and clinical investigations and also the ethnopharmacological history of plants indicated that phytochemicals of these plants exhibit many interesting findings including antimicrobial, antioxidant, antidiabetic, antitumor, anti-inflammation, antiosteoporosis, immunobiological activities and wound healing properties.

However, there are limited studies conducted to assess the wound healing ability of these phytochemicals separately. Hence, the exact phytochemical constituents in the plant extracts that contribute for wound healing is still unclear. This inevitably also entails that the mechanisms of action these phytochemicals in wound healing have not been elucidated yet. Hence, present study is planned to evaluate mechanism of action of wound healing properties of the bioactive compounds present in *T. cordifolia* independently. Furthermore, development and formulation of transdermal patch by using one of these phytochemicals or bioactive fraction present in *T. cordifolia.*

SCOPE OF THE STUDY

Wound healing is very complex and highly regulated process; in certain circumstances or with numerous disease processes, this regulated process of wound healing can be affected result in non-healing and chronic wounds and these are a significant healthcare problem in medical practice. Presently there are various novel drug delivery systems as wound dressings, various synthetic molecules are also available as a treatment such as topical antibiotics or growth factor etc.

Among other healing treatment there is an increasing interest of medicinal plants because of their low side effects and cheaper than other marketed product.

The present investigation is focused on wound healing property of bioactive compounds present in plant *T. cordifolia* and formulation of herbal transdermal patch as a drug delivery system. Verities of phytochemicals or bioactive compound such as terpenoids, alkaloids, lignans, steroids and others having antimicrobial, antioxidant, anti-inflammation and wound healing properties. However, exact molecular mechanism of action of these bioactive compounds or phytochemicals responsible for healing of wound is still unclear.

Transdermal patches has been studied for wound healing potential; however, transdermal patch containing bioactive fraction from *T. cordifolia* need to be concentrated because bioactive fraction from *T. cordifolia* has significant wound healing potential.

RATIONALE OF PROPOSED WORK

Presently, wound treatment remains a challenge to the medical practice worldwide because of the complexities of the wound healing process. Topical therapy continues to be one of the pillars for wound healing. For wound healing lots of systemic drug are available with some advantages and disadvantages. To overcome these disadvantages now a day research is moving towards noverl drug delivery systems with incorporation of use of medicinal plants.

The present investigation is focused on the formulation and development of targeted drug delivery system that is transdermal patch for the acute and chronic wound healing. These transdermal patches will formulate by using bioactive compounds presents in T. cordifolia as they have antimicrobial, antioxidant, antidiabetic, antitumor, anti-inflammation, antiosteoporosis, immunobiological activities and wound healing properties.

LITERATURE REVIEW

A significant data amount of data collected in a literature survey which highlighting wound healing activity of T. cordifolia in normal patient as well as in specified disease condition. The survey also shown novel drug delivery system that is transdermal patch also has potential in wound healing in presence of bioactive compounds of natural origin (herbal formulation).

Barua C et al (2010) in their finding they evaluate the wound healing activity of methanolic extract of Azadirachta Indica (Neem) and T. cordifolia (Guduchi) in rats. They said that early reepithelization and faster wound closure is possibly associated with increased keratinocyte proliferation and migration to the wound surface. An increase in tensile strength was also noted. Proliferation of fibrous connective tissue and angiogenesis was noted.

Shanbhag T et al., The present study was aimed at evaluating the wound healing profile of alcoholic extract of T. cordifolia and its effect on dexamethasone suppressed healing.

P. Sharma et al (2019) the plant reported containing chemical compound including Alkaloids, Terpenoids, Lignans, Steroids and others that establish the phytochemistry and pharmacological activity of Tinospora cordifolia. The present review highlights the pharmacological importance viz antioxidant activity, antimicrobial activity, antibacterial activity, antifungal activity, anti-

diabetic activity, antistress activity, hypolipidaemic effect, hepatic disorder, anticancer anti HIV potential, antiosteoporotic effects, antitoxic effects, wound healing, anticomplementary activity, and immunomodulating activity, systemic infection and Parkinsons disease.

Nema A et al (2012) they also evaluate the wound healing activity of T. cordifolia. In their finding they said that there was a higher percentage of wound closure in comparison to standard.

Singh AK et al (2017) they did comparative evaluation of wound healing activity of T. cordifolia. They observed that methanolic extract of T. cordifolia enhances the rate of wound healing. However, the wound healing ability of the combination of topical insulin and T. cordifolia extract was more significant than the extract alone.

Meravanige G et al (2012) they said that there was significant effect of topical T. cordifolia on healing of burn wounds in wistar rats as compared to control group of animals.

Michele F et al (2021) in this review they said that T. cordifolia and T. crispa possess significant wound healing abilities regardless of the part of the plants, extraction methods and wound models used. This review deduced the potential gaps for future research aiming to study the genus Tinospora as a potential wound healing agent.

Ravichandiran V et al (2015) they shown that formulation of transdermal patch containing bioactive fraction from the bark of *Ficus racemose* having wound healing potential

Kataria K et al they performed in vivo wound healing performance of drug loaded electrospun composite nanofibers transdermal patch with the help of this they obtained a sustained and controlled drug release.

Mendes A C et al performed experiment on hybrid electrospun chitosan-phospholipids nanofibers for transdermal drug delivery and they found that resulted nanomembrane of the drug and excipient were stable as well as release of drugs was significant.

Mohd Zuki S A et al (2018) in this overview they said that one can use nanocrystal cellulose as drug excipient in transdermal patch for wound healing.

Mehmat et al (2020) in this review, researcher address the problems in management while treatment for acute and chronic wounds. They also demonstrate the pathophysiology, etiology,

prognosis and microbiology of wounds. They also introduced pharmaceutical technology as part of wound management aiming to assist health professionals to overcome the current implications on wound assessment. In addition, authors review researches which included the use of gels and dermal films as wound healing agents. It can be said that natural and synthetic drugs or carriers provide promising solutions in order to meet the wound management standards.

Hassan s, Ali M, Mir M et al (2021) they developed and evaluated drug delivery patch for topical wound healing application.

Aim: Formulation, Development and Evaluation of herbal transdermal patch using different bioactive compounds for acute and chronic wound healing.

Objectives of research:

The present work undertaken with following objectives:

1. To evaluate wound healing ability of bioactive compounds present in *T. cordifolia* independently.
2. To isolate targeted bioactive compound that contribute to wound healing.
3. To evaluate the exact molecular mechanism of action of bioactive compound that responsible for wound healing process.
4. Formulation and development of transdermal patch containing bioactive compound from *T. cordifolia*.
5. Evaluation of formulated herbal transdermal patch

MATERIALS AND METHODS

a) Material

1. Plant material: In the present will collect sample of plant from local region Aurangabad, Maharashtra, India.

2. Animals: Will select healthy albino mice of either sex (weighing 35 to 40 gms) for wound healing activity.

b) Methodology

1. Extraction

Preferably the soxhlet extraction method was used with methanol as the solvent.

2. Isolation bioactive compounds
3. Analytical study of isolated compounds
4. Formulation of transdermal patches

Transdermal patches will be prepared by suitable method (eg. Drug loaded matrix)

5. Pre-formulation evaluation of transdermal patch.
6. Evaluation of formulated patches

The transdermal patches will be evaluated for in-vitro and in-vivo tests. In the evaluation of transdermal patches includes thickness, weight uniformity, folding endurance, percentage moisture content, water vapor permeability, drug content, in-vitro permeation of the fractions and in-vitro cytotoxicity.

7. Wound healing activity by using suitable animal model (eg. Excision wound model or incision wound healing)

RESEARCH WORK PLAN

- **Literature Survey**
- **Isolation and Collection of bioactive compounds**
- **Pre-formulation studies**

Formulations:

- **Preparation of herbal transdermal patch**
- **Evaluation of transdermal patch**

  - Thickness
  - weight uniformity
  - folding endurance
  - percentage moisture content
  - water vapor permeability
  - drug content
  - in-vitro permeation of the bioactive compounds
  - in-vitro cytotoxicity

- **Study of wound healing activity of prepared herbal transdermal patch using animal model**
- **Statistical analysis and interpretation of data**
- **Conclusion of the obtained results**

PROPOSED WORK PLAN/ FORMULATION AND STRUCTURE OF STUDY

Year-wise Plan of work and targets to be achieved:

Sr. No.	Expected target to be achieved	1-6 months	7-10 months	11-22 months	22--27 months	28- 33 months	34-36 Month
01	Literature survey	Literature survey					
02	Isolation and collection of bioactive compound	Extraction and collection of drug and excipients					
03	Formulation, development and optimization	Formulation, development and optimization					
04	Evaluation	Evaluation					
05	In-vivo study	In-vivo study					
06	Statistical Analysis, Data Interpretation and Conclusions	Statistical Analysis, Data Interpretation and Conclusions					
07	Publishing Research and submitting data	Publishing Research and submitting data					

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